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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/932,166	08/17/2001	Aya Jakobovits	511582006000	4666

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EXAMINER	
SAUNDERS, DAVID A	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 09/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/932,166	JAKOBOVITS, AYA	
	Examiner	Art Unit	
	David A Saunders, PhD	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 April 2004 and 22 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-18,20,22,24 and 27-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-18,20,22,24,27-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/1704*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/26/04 has been entered.

Following entry of the amendment of 4/26/04, claims 1, 4-18, 20, 22, 24 and 27-31 are pending and under examination.

Claim 1 is objected to because of the following informalities: In claim 1 the amendment markings are confusing at lines 14, 15 and 17. In each case applicant appears to be deleting a comma and adding a semicolon; however, square brackets surround these markings. These brackets indicate deletion; thus there are no punctuation marks at these points. Like objections apply to claim 20, at lines 13 and 15. Appropriate correction is required.

The following prior art rejections of record are maintained.

Claims 1, 4, 6-7, 10-12, 14-15, 18, 20, 22 and 29-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jakobovits et al in view of Edleman et al (Meth Enzymol) and Edleman et al (3,843,324).

The essentials of the rejection previously stated on 4/21/03 are set forth as follows.

Jakobovits et al. show experiments which have all aspects of the instant invention, except that 1) they use nonnucleated cells (erythrocytes) instead of nucleated

cells, 2) they use surface treated cells (treated with neuraminidase), and 3) they use a lectin as a ligand (lectin appears to be excluded at specification para. [22] but not in the claim).

With respect to the use of nucleated cells, Jakobovits et al. teach that their method has been extended to isolating lectin receptors from lymphocytes, which are nucleated cells (page 489, last para.). Also Edelman et al. teach a like method of binding cells with their receptors to a solid support that has been derivative with a ligand of the receptor. After washing of the support, the bound cells are mechanically removed form the derivatized support by plucking. See Figure 1 and text description thereof at pages 198+. Edelman et al. teach that such methods can be used to bind nucleated cells to the derivatized support. See teaching of various hematopoietic lineage cells, such as lymphocytes and thymocytes at pages 205-207 and 212-220.

With respect to the use of surface treated cells, none of the methods used by Edelman et al. for the isolation of lymphoid cells (e.g. page 205) employ a detergent, enzyme or other agent that would render the cells as "surface-treated."

Regarding the use of ligands which are not lectins, Jakobovits et al. teach that their method should be extendable to the study of receptors other than those for lectin. They suggest such receptors for hormones, toxins and antigens (page 1489). Also Edelman et al. teach that antigens or antibodies, as well as lectins, are used to derivatized the solid support. See page 198. They exemplify use of antigen at pages 207 and 212-220. They also suggest other ligands such as hormones or antibodies to cell surface antigens (para. spanning pages 220-221).

From the above considerations of the two references, it is clear that one would have fully expected that the method of Jakobovits et al. would be extended from the use of a lectin as a ligand, to bind erythrocytes treated with neuraminidase, to the use of numerous other types of ligands, to bind nucleated cells which have not been surface-treated." Claim 1, thus would have been obvious.

The combination of Jakobovits et al. with Edelman et al. is deemed proper. Jakobovits et al. teach isolation of the ligand receptor complexes from the cells –i.e. they are interested isolation of the ligand receptor complexes that are retained on the solid support after the cells have been sheared therefrom. Edelman et al. teach isolation of the cells bearing a particular receptor –i.e. they are interested in the cells that are sheared from the solid support. Despite this difference the references are properly combinable. Note that Edelman et al. teach that the method may be used for "isolation of cell surface markers", as well as for the separation of cells (page 195). This provides a nexus between Jakobovits et al. and Edelman et al.

With respect to the inserted recitation of "wherein the microenvironment includes additional non-covalently associated cellular components" the examiner does not give this patentable weight in overcoming the prior art for the reason that the examiner finds nothing in the instant disclosure which distinguishes applicant's methodology from that employed by Jakobovits et al or either of the Edleman et al references. In each case a shearing force of some sort is employed to provide the "force sufficient to dissociate the receptor and its microenvironment from the membrane". The instant disclosure is devoid of any teachings, which teach that the force applied is quantitatively different in

intensity and/or duration than that applied in the prior art. The office therefore reasonably considers that what Edleman et al taught inherently achieved the separation of the antigen receptor, along with its "microenvironment", from the membrane of lymphoid cells.

With respect to applicant's particular arguments, note the following.

Applicant urges (page 8) that Jakobovits et al show nothing more than lectin/oligosaccharide interactions on enzymatically treated red blood cells (RBC), and that all else is merely a suggestion of other applications. The office notes that the last paragraph of page 1489 commences with the statement, in the present tense, "We are now applying this technique for the isolation of lectin receptors from lymphocytes." This is a statement of what was being done at the time of the reference. If the authors wanted recognition for what they were doing at the time of publication, it is now self-serving for one of the authors to argue that there would be no expectation of success for applying the method to nucleated cells, such as lymphocytes.

Applicant has urged (also on page 8) that lectin – oligosaccharide interactions do not predict antigen, hormone, or toxin interactions with a discrete cell surface receptor and has urged that Jakobovits et al teach an "artificial" ligand receptor binding system (by virtue of there use of surface treatment of the cells). The office finds this argument unconvincing because Edleman et al have been successful in employing antigen to bind lymphoid cells, that carry discrete antigen receptors (i.e. cell surface immunoglbulins) to a solid phase and in plucking the cells therefrom. As noted supra these were not

"artificial" cells treated with an enzyme. As to the capability of isolating a receptor in its membrane microenvironment by the method of Edleman et al, see further infra.

Applicant has urged that the disclosure of Edleman et al (Meth. Enzymol.) is directed to the isolation of cells and, except for a mere mention of isolation of receptors, fails to teach isolation of receptors with their associated microenvironment (page 9). Applicant has further urged that Edleman et al teach away from the removal of receptors from the cell surface, by virtue of the fact that Edleman et al's fractionated cells can be successfully subjected to a second round of fiber fractionation, due to the receptors that remain on their cell surface; and applicant has urged that Figure 1's depictation of membrane fragment with receptor bound to ligand on the fiber has not been shown by objective evidence (para. spanning pgs 9-10 and para. spanning pgs 11-12).

The examiner considers that while Edleman et al did not analyze what remained on the fiber after release of the cells, the full teachings of the article, even at the points noted by applicant, are consistent with the depictation in Figure 1 of a fragment of membrane with receptor remaining on the fiber, after release of the cells therefrom. Firstly, Edleman et al teach (para. spanning pgs. 208-209) that the shearing/plucking of cells from the fiber "may produce a lesion in the cell surface membrane", and they further teach this effect particularly occurs" if the fiber is heavily derivatized" (i.e. derivatized with ligand). Edelman et al ('324) provide like teachings at col. 2, line 64 – col. 3, line 7. Therefore, even though both Edleman et al references were primarily directed to isolating viable intact cells having minimal membrane damage, these

references provided enabling direction (by teaching one to increase the density of ligand attached to the fiber) to one who wanted to isolate receptors of nucleated cells, as suggested by Edleman et al at 'page 195, or by Jakobovits et al at page 1489.

Secondly, Edleman et al teach (pg 209) that viability of pluncked cells can be increased when the cells are incubated for 30 min. at 37 deg. in the presence of serum. They consider this result as "suggesting that the cells are repairing lesions in their surface membranes".

Thirdly, applicant's argument that the fiber fractionated cells can successfully under go a further round of fiber fractionation cannot be taken to prove that no portion of the membrane, with associated receptor was lost in the first round. Figures 4 and 5 (actual photomicroscopic views, not artist's drawings) show only a small portion of the cell surface adheres to the ligand derivatized fiber; one would expect the remainder of the membrane to also have receptors.

Therefore, while Edleman et al's figures and teachings may be suggestions, rather than convincing proofs, these teachings nevertheless provide one with enough motivation to employ the fiber fractionation method to isolate membrane fragments, bearing cell surface receptors, from unselected cells, such as lymphocytes. Further, their teachings provide direction to one of skill (increase the ligand density). Though success in the use of fiber fractionation may not have been assured, all that is required for obviousness is a reasonable expectation of success. In re O'Farrell 7 USPQ 894.

Applicant has urged (pgs 9-10) that the "plucking" method of Edleman et al is distinct from the "Plucking" method instantly. This argument is unconvincing because

there is no claim limitation that would distinguish. Also, as noted supra, the specification is devoid of any teachings that would distinguish the nature of the instant plucking/ shearing force from that of Edleman et al, in terms of magnitude and/or duration.

Applicant has additionally urged (pg. 10-11) that Jakobovits et al do not enable the removal of the receptor from the support and that the teachings of the results obtained with the SDS – page analysis merely point to artifacts. These arguments are self – serving, since the inventor was an author who now wants the article to not teach something that it did teach. Page 1484 clearly teaches that the plucking method is better than the detergent disruption method, which removes receptors from their "microenvironment". The sentence spanning pages 1484-1485 teaches how to release the receptors with the use of a free ligand; this is precisely how applicant contemplates the removal of the receptor from the solid phase ligand, in the case where applicant refers to "competitively dissociating the ligand /receptor complex" (para. [0041]).

The issue of whether or not Jakobovits et al were analyzing the presence of truly associated membrane proteins or merely artifacts in their SDS-PAGE experiments is not deemed material. The concluding claim step of "analyzing the microenvironment of the receptor" has been disclosed as having great breadth, and it would include the case of finding nothing associated with the receptor (see para. [0009], [0013], [0028] for example). In any type of further analysis, one of skill would expect the requirement to distinguish artifact from meaningful results. Given the fact that "analyzing the microenvironment" requires no particular step to be conducted and requires no

particular result to be obtained, the teachings of SDS-PAGE analysis by Jakobovits et al are consistent with what is recited.

Applicant urges (page 11) that differences in membrane fluidity between RBCs and nucleated cells would not lead one to expert the results of Jakobovits et al to be extendable to nucleated cells. Applicant is reminded, however, that Jakobovits et al report, in the present tense, that "We are now applying this technique for the isolation of lectin receptors from lymphocytes –i.e. something is being done with lymphocytes. Their teachings about extension of the method to receptors of hormones, toxins, and antigens are taken to be their statement of a reasonable expectation of success. If applicant wants the reference to show these additional isolations could be done without doubt as to the outcome, then the citation would have been under 102, over Jakobovits only.

Applicant concludes (page 12) by arguing that all of Edleman et al's teachings at pages 208-209 regarding the forming of a lesion in the cell membrane and the repair thereof by incubation with serum, are merely suggestions. As noted supra, the examiner considers these teachings provide enough for one of skill to have a reasonable expectation of success.

Applicant's arguments filed on 4/26/04 have been fully considered but they are not persuasive. Applicant's urgings concerning tertiary references have not separately argued their teachings. Therefore the following rejections are repeated without further consideration of applicant's urgings.

Claims 8, 16, 24 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jakobovits et al in view of Edleman et al. as applied to claims 1, 20 and 22 above, and further in view of Chang (WO 84/03151).

Claims 5, 9, 27 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jakobovits et al in view of Edleman et al. as applied to claims 1, 20 and 30 above, and further in view of Kupchik.

Claims 5 and 31 have been added since the monoclonal antibodies of Kupchik would be used on tumor cells.

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jakobovits et al in view of Edleman et al as applied to claim1 above, and further in view of Seifert et al (5,721,120).

With respect to the above cited prior art, independent claims 17 and 28 are allowable.

Since application 10/209,325 is copending and it is impossible to determine which might be in condition for allowance first, the double patenting rejection is maintained, but could be withdrawn if the instant case is the first to be in condition for allowance M.P.E.P. 804.

Claims 1, 4-18, 20, 22, 24, and 27-31 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 16-25 and 28-31 of copending Application No. 10/209,328. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass common subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Saunders whose telephone number is (571) 272-0849. The examiner can normally be reached on Monday to Thursday from 8 AM to 5:30 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Saunders/LR
September 3, 2004